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WO 01/98274 A2

(54) Title: SULPHONAMIDE DERIVATIVES

(57) Abstract:

SULPHONAMIDE DERIVATIVES

This invention relates to a series of sulphonamides, to processes for their preparation, to pharmaceutical compositions containing them, and to their use in medicine.

The cyclic nucleotides cAMP and cGMP are known to be responsible for the regulation of a variety of intracellular processes. The levels of these nucleotides are modulated by the stimulation of adenylate or guanylate cyclases and by the activity of phosphodiesterase enzymes. Phosphodiesterases (PDEs) specifically convert cyclic nucleotides to inactive analogues. Eleven PDE gene familes have been identified to date, based on substrate specificity and regulatory characteristics. PDE7 is a low K_M cAMP specific enzyme which is insensitive to the standard PDE4 inhibitor, rolipram. PDE7 is thought to play an important role in T cell activation [Beavo *et al*, Science (1999), 283: 848], which implies that inhibitors of PDE7 should have benefit in T cell mediated diseases. In addition, PDE7 has been detected in airway epithelial cells [Barnes *et al*, Am. J. Respir. Cell Mol. Biol. (1999) 20: 292] so inhibitors should be beneficial in diseases of the airway.

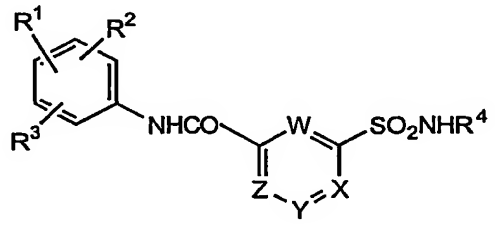
We have now found a series of sulphonamides which are potent and selective inhibitors of PDE7. The compounds are thus of use in the prophylaxis and treatment of diseases in which inhibition of PDE7 can have a therapeutic benefit.

Certain sulfonamide amide compounds are generally disclosed in International Specification No. WO-A-9938845 as modulators of PPARγ activity.

International Specification No. WO-A-9932433 also generally discloses certain sulfonamide amide compounds for use as inhibitors of 15-lipoxygenase.

International Specification No. WO-A-0052144 specifically discloses the use of 3-(4-bromophenylsulfamoyl)-*N*-(3-nitrophenyl)benzamide as an ecto-phosphatase inhibitory molecule.

Thus according to one aspect of the invention we provide a compound of formula (1):



(1)

wherein

W, X, Y and Z which may be the same or different, each represents a nitrogen atom or a $C(R^5)$ group [in which R^5 is a hydrogen or halogen atom or an alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, $-NO_2$ or -CN group] provided that two or more of W,X,Y and Z are $C(R^5)$ groups;

R^1, R^2 and R^3, which may be the same or different, each is an atom or group $-L^1(Alk^1)_rL^2(R^6)_s$ in which L^1 and L^2, which may be the same or different, is each a covalent bond or a linker atom or group, r is zero or the integer 1, Alk^1 is an aliphatic or heteroaliphatic chain, s is an integer 1, 2 or 3 and R^6 is a hydrogen or halogen atom or a group selected from alkyl, $-OR^7$ [where R^7 is a hydrogen atom or an optionally substituted alkyl group], $-SR^7$, $-NR^7R^8$ [where R^8 is as just defined for R^7 and may be the same or different], $-NO_2$, -CN, $-CO_2R^7$, $-SO_3H$, $-S(O)R^7$, $-SO_2R^7$, $-OCO_2R^7$, $-CONR^7R^8$, $OCONR^7R^8$, $-CSNR^7R^8$, $-OCR^7$, $-OCOR^7$, $-N(R^7)COR^8$, $-N(R^7)CSR^8$, $-S(O)NR^7R^8$, $-SO_2NR^7R^8$, $-N(R^7)SO_2R^8$, $-N(R^7)CON(R^8)(R^9)$ [where R^9 is a hydrogen atom or an optionally substituted alkyl group], $-N(R^7)CSN(R^8)R^9)$, $-N(R^7)SO_2N(R^8)(R^9)$, $-C(R^7)=NO(R^8)$, cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group]; provided that one or more of R^1, R^2 or R^3 is a substituent other than a hydrogen atom;

R^4 represents an optionally substituted phenyl, 1- or 2- naphthyl, pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl group;

and the salts, solvates, hydrates and N-oxides thereof;
provided that the compound of formula (1) is not 3-(4-bromophenylsulfamoyl)-*N*-(3-nitrophenyl)benzamide.

Optional substituents present on groups represented by R^4 include one, two, three or more groups, each represented by the group R^{4a}, where R^{4a} is a $-L^1(Alk^1)_rL^2(R^6)_s$ group as generally defined above and more specifically described hereinafter provided that $-L^1(Alk^1)_rL^2(R^6)_s$ does not represent -H. Where more than one R^{4a} substituent is present, these may be the same or different.

In compounds of the invention, when a pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl group represented by R^4 is present it is linked to the remainder of the compound through any available carbon atom in the R^4 ring.

When in the compound of formula (1) L^1 and/or L^2 is present as a linker atom or group in a substituent R^1, R^2, R^3 and/or R^{4a}, each L^1 and/or L^2 group may be for example an -O- or -S- atom or a -C(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^{10})-$ [where R^{10} is a hydrogen atom or a C_{1-6} alkyl, e.g. methyl or ethyl, group], $-CON(R^{10})-$, $-OC(O)N(R^{10})-$, $-CSN(R^{10})-$, $-N(R^{10})CO-$, $-N(R^{10})C(O)O-$, $-N(R^{10})CS-$, $-SON(R^{10})-$, $-SO_2N(R^{10})-$, $-N(R^{10})SO_2-$, $-N(R^{10})CON(R^{10})-$, $-N(R^{10})CSN(R^{10})-$, $-N(R^{10})SON(R^{10})-$ or $-N(R^{10})SO_2N(R^{10})-$ group. Where the linker group contains two R^{10} substituents these may be the same or different.

When Alk^1 is present in the compounds of the invention it may be a C_{1-10} aliphatic chain, for example a straight or branched chain C_{1-6}alkylene, e.g. C_{1-3}alkylene, C_{2-6}alkenylene, e.g. C_{2-4}alkenylene, or C_{2-6}alkynylene, e.g. C_{2-4} alkynylene chain. Each of said chains may be optionally interrupted by one or two heteroatoms or heteroatom-containing groups represented by L^3 [where L^3 is an atom or group as just described for L^1], to form an Alk^1 heteroaliphatic chain.

Particular examples of aliphatic chains represented by Alk^1 include $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_2CH_2-$, $-CH(CH_3)CH_2-$, $-(CH_2)_3CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2-$, -CHCH-,

-CHCHCH$_2$-, -CH$_2$CHCH$_2$-, -CHCH(CH$_2$)$_2$-, -CH$_2$CHCHCH$_2$-, -(CH$_2$)$_2$CHCH$_2$, -CC-, -CCCH$_2$-, -CH$_2$CC-, -CC(CH$_2$)$_2$-, -CH$_2$CCCH$_2$-, or -(CH$_2$)$_2$CC- chains. Where appropriate each of said groups may be optionally interrupted by one or two atoms and/or groups L^3 to form a heteroaliphatic chain.

When the substituent R^6 is present in compounds of formula (1) as a halogen atom it may be for example a fluorine, chlorine, bromine or iodine atom.

Alkyl groups represented by the group R^6 include straight or branched C_{1-6} alkyl groups, e.g. C_{1-3}alkyl groups such as methyl or ethyl groups.

Optionally substituted alkyl groups represented by R^7, R^8 and/or R^9 in compounds of the invention include those alkyl groups just mentioned for R^6 optionally substituted by one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxy or C_{1-3} alkoxy e.g. methoxy or ethoxy groups.

When R^6 is present in compounds of formula (1) as a cycloaliphatic group it may be an optionally substituted C_{3-10} cycloaliphatic group. Particular examples include optionally substituted C_{3-10}cycloalkyl, e.g. C_{3-7} cycloalkyl or C_{3-10} cycloalkenyl e.g. C_{3-7} cycloalkenyl groups.

Heterocycloaliphatic groups represented by R^6 include the cycloaliphatic groups just described for R^6 but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups represented by L^4, where L^4 is an atom or group as described above for L^1.

Particular examples of R^6 cycloaliphatic and heterocycloaliphatic groups include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 3,5,-cyclohexadien-1-yl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-

pyrazolinyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, homopiperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5,2-oxadiazinyl groups.

Optional substituents which may be present on R^6 cycloaliphatic and heterocycloaliphatic groups include one, two, three or more substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, C_{1-6}alkyl, e.g. methyl or ethyl, C_{1-6}alkoxy, e.g. methoxy or ethoxy or hydroxyl groups. The heterocycloaliphatic groups may be attached to the remainder of the molecule of formula (1) through any appropriate ring carbon or heteroatom.

Aryl groups represented by the group R^6 include for example mono- or bicyclic C_{6-12} optionally substituted aromatic groups, for example optionally substituted phenyl, 1– or 2–naphthyl, or indenyl groups.

Heteroaryl groups represented by R^6 include for example C_{1-9} optionally substituted heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaryl groups represented by R^6 include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl,

pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl.

The aryl or heteroaryl groups represented by R^6 may be attached to the remainder of the molecule of formula (1) through any available ring carbon or nitrogen atom as appropriate.

Optional substituents present on the aryl or heteroaryl groups represented by R^6 include one, two, three or more aroms or groups as described generally above and specifically below in relation to the group R^5. Where more than one substituent is present, these may be the same or different.

Where more than one atom or group R^6 is present in $-L^1(Alk^1)_rL^2(R^6)_s$ [i.e. where s is an integer two or three] it is understood that each R^6 atom or group may be the same or different and may be attached to the same or different atoms, particularly for example to form groups such as $Alk^1(R^6{}_2)$or $-Alk^1(R^6)_3$.

Particular examples of substituents represented by R^1, R^2 and/or R^3 in compounds of the invention include hydrogen and halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, haloC_{1-6}alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. $-C(OH)(CF_3)_2$, C_{1-6}alkoxy, e.g. methoxy or ethoxy, haloC_{1-6}alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C_{1-6}alkylthio e.g. methylthio or ethylthio, or $-(Alk^1)_rR^{6a}$ groups in which Alk^1 is a straight or branched C_{1-3}alkylene chain, r is zero or an integer 1 and R^{6a} is a -OH, -SH, $-N(R^7)(R^8)$, -CN, $-CO_2R^7$, $-NO_2$, $-CON(R^7)(R^8)$, $-CSN(R^7)(R^8)$, $-COR^7$, $-N(R^7)COR^8$, $-N(R^7)CSR^8$, $-SO_2R^7$, $-SO_2N(R^7)(R^8)$, $-N(R^7)SO_2R^8$, $-N(R^7)CON(R^8)(R^9)$, $-N(R^7)CSN(R^8)$, $-N(R^7)SO_2N(R^7)(R^8)$, $-C(R^7)=NO(R^8)$ or optionally substituted cyclopentyl, cyclohexyl, cyclopentyloxy, cyclohexyloxy, phenyl, phenoxy,

benzyloxy, pyridyl, pyrimidinyl or tetrazolyl group. The same substituents, other than a hydrogen atom may be present as R^{4a} atoms or groups in compounds of the invention.

When R^5 is present in compounds of formula (1) as a halogen atom it may be for example a fluorine, chlorine, bromine or iodine atom.

Alkyl groups represented by the groups R^5 in compounds of the invention include straight or branched C_{1-6}alkyl groups as described above for the group R^6. Haloalkyl groups represented by R^5 include those alkyl groups just mentioned substituted by one, two or three halogen atoms, e.g. fluorine or chlorine atoms. Particular examples include $-CH_2F$, $-CHF_2$ and $-CF_3$ groups.

Alkoxy groups represented by R^5 include straight or branched C_{1-6}alkoxy groups, e.g. C_{1-3}alkoxy groups such as methoxy or ethoxy groups. Haloalkoxy groups represented by R^5 include those just mentioned alkoxy groups substituted by one, two or three halogen atoms, e.g. fluorine or chlorine atoms. particular examples include $-OCH_2F$, $-OCHF_2$ and $-OCF_3$ groups.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

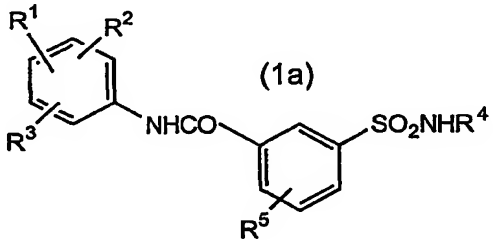
Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as

magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

It will be appreciated that where compounds of formula (1) exist as geometrical isomers and/or exantiomers or diastereomers then the invention extends to all such isomers of the compounds of formula (1), and to mixtures thereof, including racemates.

In the compounds according to the invention, each of W, X, Y and Z is preferably a C(R^5) group. One particular group of compounds of this type has the formula (1a):

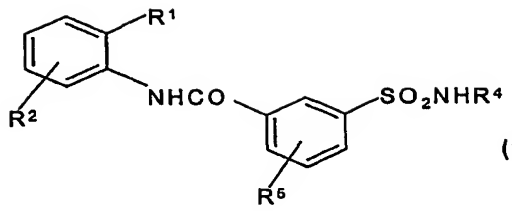


(1a)

(1a)

wherein R^1, R^2, R^3, R^4 and R^5 are as generally and particularly defined herein for compounds of formula (1) and the salts, solvates, hydrates and N-oxides thereof.

In general in compounds of formulae (1) and (1a) R^4 is preferably a phenyl, 1- or 2-naphthyl, pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl group optionally substituted by one or two R^{4a} substituents as defined herein. Especially preferred is when R^4 is substituted by one or two R^{4a} substituents. In one particular group of compounds of the invention R^4 is a substituted phenyl, 1-naphthyl or pyridyl group. In compounds of this type and in general in compounds of the invention R^3 is in particular a hydrogen atom. One particular class of compounds of this later type has the formula (1b):



(1b)

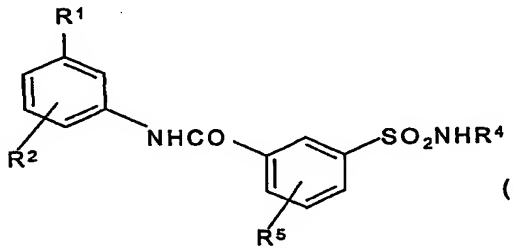
wherein R^2, R^4 and R^5 are as generally and particularly defined herein for compounds of formula (1);

R^1 is a substituent, other than a hydrogen atom, as defined herein for compounds of formula (1);

and the salts, solvates, hydrates and N-oxides thereof.

Compounds of formula (1b) in which R^2 is a hydrogen atom form a further particular class of compound according to the invention. A further class of compounds according to the invention has the formula (1b) in which R^2 is a methoxy group.

Another particular class of compounds has the formula (1c):



(1c)

wherein R^2, R^4 and R^5 are as generally and particularly defined herein for compounds of formula (1);

R^1 is a substituent, other than a hydrogen atom, as defined herein for compounds of formula (1);

and the salts, solvates, hydrates and N-oxides thereof.

Compounds of formula (1c) in which R^2 is a hydrogen atom form a further particular class of compound according to the invention.

In compounds of the invention R^5 is preferably a hydrogen atom.

R^1 in compounds of the invention is preferably a fluorine, chlorine, bromine or iodine atom, or a methyl, ethyl, difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, $-N(R^7)(R^8)$, -CN, $-CO_2R^7$, $-NO_2$, $-CON(R^7)(R^8)$, $-COR^7$, $-SO_2R^7$, $-SO_2N(R^7)(R^8)$, $-C(R^7)=NO(R^8)$, pyridyl, or tetrazolyl group. R^7 and R^8, which may be the same or different, are preferably a hydrogen atom or an alkyl group. Particularly preferred R^1 substituents are $-CO_2H$, $-NO_2$ or tetrazolyl groups.

R^4 in compounds of the invention is preferbaly substituted with one or two R^{4a} substituents selected from fluorine, chlorine, bromine or iodine atoms, or methyl, ethyl, difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy, trifluoromethoxy, $-N(R^7)(R^8)$, -CN, $-CO_2R^7$, $-NO_2$, $-CON(R^7)(R^8)$, $-COR^7$, $-SO_2R^7$ or $-SO_2N(R^7)(R^8)$ groups. R^7 and R^8, which may be the same or different, are preferably a hydrogen atom or an alkyl group. Especially preferred R^{4a} substituents are fluorine, chlorine, bromine or iodine atoms, or methyl, ethyl, trifluoromethyl, $-CO_2C(CH_3)_3$, $-CONH(CH_2CH_3)$, or $-CONH(C(CH_3)_2)$ groups.

One particular group of compounds of the invention includes:
4-[3-(2-nitrophenylcarbamoyl)benzenesulfonylamino]benzoic acid *tert*-butyl ester;
4-[3-(2-nitrophenylcarbamoyl)benzenesulfonylamino]benzoic acid ethyl amide;
2-[3-(4-chloro-3-nitrophenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(4-chloro-2-methylphenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(2-bromo-5-trifluoromethylphenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(2-chloro-4-trifluoromethylphenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(2,4-dimethylphenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(4-bromophenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(4-bromo-2-trifluoromethylphenylsulfamoyl)benzoylamino] benzoic acid;
2-[3-(2,4-dichlorophenylsulfamoyl)benzoylamino]benzoic acid;

2-[3-(2-chloro-4-methylphenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(4-chloronaphthalen-1-ylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(4-ethylcarbamoyl-2-methylphenylsulfamoyl)benzoylamino]
benzoic acid;
3-[3-(4-chlorophenylsulfamoyl)benzoylamino]benzoic acid;
and the salts, solvates, hydrates and N-oxides thereof.

Another particular group of compounds of the invention includes:
2-[3-(4-bromo-2-ethylphenylsulfamoyl)-benzoylamino]benzoic acid;
2-[3-(2-methyl-6-trifluoromethyl-pyridin-3-ylsulfamoyl)benzoylamino]
benzoic acid;
2-[3-(4-chlorophenylsulfamoyl)benzoylamino]benzoic acid;
2-({1-[3-(3-chlorophenylsulfamoyl)phenyl]methanoyl}amino)benzoic acid;
2-({1-[3-(4-trifluoromethylphenylsulfamoyl)phenyl]methanoyl}amino)-
benzoic acid;
2-[3-(2-methyl-4-fluorophenylsulfamoyl)benzoylamino]benzoic acid;
5-methoxy-2-({1-[3-(4-trifluoromethylphenylsulfamoyl)-phenyl]-
methanoyl}amino)benzoic acid;
2-[3-(2-methyl-5-trifluoromethylphenylsulfamoyl)benzoylamino]benzoic
acid;
and the salts, solvates, hydrates and N-oxides thereof.

Compounds according to the invention are potent inhibitors of PDE7. The ability of the compounds to act in this way may be simply determined by employing a test such as those described in the Examples hereinafter.

The compounds according to the invention are of particular use in the prophylaxis and treatment of diseases in which in which inhibition of PDE7 can have a therapeutic benefit for example in autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus, in transplant rejection, in graft v host disease, psoriasis, in pannus formation in rheumatoid arthritis, restenosis following angioplasty and atherosclerosis, in osteoporosis and in diseases in which cells receive pro-inflammatory signals such as asthma, inflammatory bowel disease,

pancreatitis, chronic obstructive pulmonary disease, chronic bronchitis, atopic dermatitis and allergic rhinitis.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

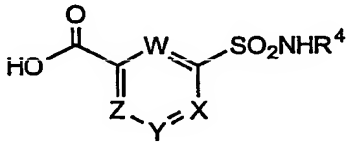
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g.

around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

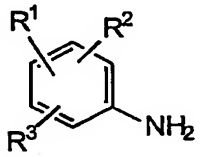
The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols R^1 to R^9, W, X, Y, Z, L^1, L^2, L^3, Alk^1, r and s when used in the text and formulae are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention, a compound of formula (1) may be prepared by coupling an acid of formula (2):



(2)

or an active derivative thereof with an aniline of formula (3):



(3)

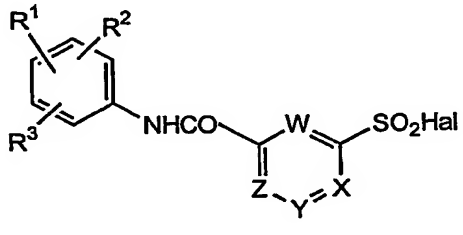
or a salt thereof.

Active derivatives of acids of formula (2) include anhydrides, esters and acid halides, e.g. acid chorides, and may be obtained by standard procedures.

The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out with an active derivative of the acid of formula (2) in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine or N,N-diisopropylethylamine, or a cyclic amine, such as pyridine or N-methylmorpholine, or a hydride, such as sodium hydride in an inert organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran or a halogenated hydrocarbon, such as dichloromethane or dichlorobenzene, at a low temperature, e.g. around -30°C to around ambient temperature.

Where an acid of formula (2) is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to reaction with the aniline of formula (3).

In a further process according to the invention, a compound of formula (1) may be prepared by reaction of a sulphonyl halide of formula (4):



(4)

Where Hal is a halogen atom such as a chlorine, bromine or iodine atom, with an amine of formula R^4NH_2 in the presence of a base, for example an

organic amine such as pyridine or triethylamine at or around ambient temperature.

The intermediate acids of formula (2) and sulphonyl halides of formula (4) may be obtained from simpler, known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions as described below and in the Examples hereinafter. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of formula (1) where appropriate functional groups exist in these compounds. Additionally, although a number of the intermediate anilines of formula (3) and amines R^4NH_2 for use in the reactions described above are known, others can be derived therefrom using these standard synthetic methods.

Thus compounds of the invention and intermediates thereto may be prepared by alkylation, arylation or heteroarylation. For example, compounds containing a $-L^1H$, $-L^1(Alk^1)_rL^2H$ or $-Alk^1L^2H$, group (where L^1 and L^2 is each a linker atom or group) may be treated with an alkylating agent $(R^6)_sL^2Alk^1X^1$ or R^6X^1 in which X^1 is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethyl-sulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydro-furan.

In another example, compounds containing a $-L^1H$, $-L^1(Alk)_rL^2H$ or $-Alk^1L^2H$ group as defined above may be functionalised by acylation or thioacylation, for example by reaction with one of the alkylating agents just

described but in which X^1 is replaced by a $-C(O)X^2$, $C(S)X^2$, $-N(R^6)COX^2$ or $-N(R^6)C(S)X^2$ group in which X^2 is a leaving atom or group as described for X^1. The reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methyl-morpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature. Alternatively, the acylation or thioacylation may be carried out under the same conditions with an acid or thioacid (for example one of the alkylating agents described above in which X^1 is replaced by a $-CO_2H$ or -COSH group) in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexyl-carbodi-imide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzo-triazole. Alternatively the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction.

In a further example compounds may be obtained by sulphonylation of a compound containing an -OH group by reaction with one of the above alkylating agents but in which X^1 is replaced by a $-S(O)Hal$ or $-SO_2Hal$ group in which Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example, compounds containing a $-L^1H$, $-L^2H$ or $-L^3H$ group as defined above may be coupled with one of the alkylation agents just described but in which X^1 is replaced by an -OH group in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate.

In a further example, ester groups $-CO_2R^7$ in the compounds may be converted to the corresponding acid [$-CO_2H$] by acid- or base-catalysed hydrolysis depending on the nature of the group R^7. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an

organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous ether or alcohol, e.g. an aqueous cyclic ether such as aqueous tetrahydrofuran or an aqueous alcohol such as aqueous methanol at an elevated temperature.

In a further example, $-OR^7$ groups [where R^7 represents an alkyl group such as methyl group] in compounds of formula (1) may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding $-OCH_2R^6$ group (where R^6 is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [$-CO_2R^7$] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in the compounds may be converted to a corresponding $-OR^7$ group (where R^7 is an optionally substituted alkyl group) by coupling with a reagent R^7OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [$-NHSO_2NH_2$] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In a further example amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohyride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [$-NH_2$] groups in the compounds may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [$-NO_2$] group may be reduced to an amine [$-NH_2$], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid. Catalytic hydrogenation is particularly useful for the preparation of intermediate amines of formula (3) from their corresponding nitro analogues.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In another example, sulphur atoms in the compounds, for example when present in a linker group L^1, L^2 or L^3 may be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a

halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

Tetrazolyl groups in the compounds may be obtained by cycloaddition using a corresponding nitrile and an azide, e.g. sodium azide, optionally in the presence of a catalyst e.g. a Lewis acid such as aluminium chloride in an aprotic solvent such as dimethylformamide at an elevated temperature.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Chromatography, recrystalliation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention.
All temperatures are in °C.
The following abbreviations are used:
TLC - thin layer chomatography; DMF - *N, N*-dimethylformamide

INTERMEDIATE 1
3-(2-Nitrophenylcarbamoyl)benzenesulfonyl chloride
A mixture of 3-(chlorosulfonyl)benzoyl chloride (1.0g), 2-nitroaniline (0.58g) and pyridine (0.68ml) in dichloromethane (20ml) was stirred under an atmosphere of nitrogen for 4.5h. The mixture was diluted with dichloromethane (30ml), washed with 2N hydrochloric acid (100ml), dried (magnesium sulfate) and the solvent removed *in vacuo* to give the title compound (1.41g) as a yellow solid.
TLC R_f 0.65 (50% ethyl acetate in hexane)

The following compound was prepared by a similar procedure.

INTERMEDIATE 2
2-(3-Chlorosulfonylbenzoylamino)benzoic acid methyl ester
Prepared from 3-(chlorosulphonyl)benzoyl chloride (2.0g) and methyl anthranilate (1.3g) to give the title compound (1.9g) as a white solid.
TLC R_f 0.7 (50% ethyl acetate in hexane)

INTERMEDIATE 3
3-(4-Chlorophenylsulfamoyl)benzoic acid
A mixture of 3-(chlorosulfonyl)benzoic acid (500mg), 4-chloroaniline (304mg) and pyridine (0.92ml) in dichloromethane (30ml) was stirred overnight at room temperature under an atmosphere of nitrogen. The mixture was diluted with dichloromethane (30ml) and washed with 2N hydrochloric acid (100ml) and water (80ml). Methanol (10ml) was added to the dichloromethane and the organic layer dried (magnesium sulfate). The solvent was removed *in vacuo* and the residue purified by wet flash

chromatography on silica eluting with 50% ethyl acetate in hexane then ethyl acetate to give the title compound (257mg) as a white solid.
TLC R_f 0.40 (ethyl acetate)

The following compound was prepared by a similar procedure.

INTERMEDIATE 4

3-(4-Trifluoromethylphenylsulfamoyl)benzoic acid

Prepared from 3-(chlorosulfonyl)benzoic acid (4.11g) and 4-aminobenzotrifluoride (2.94g) to give the title compound (5.02g) as a white solid.

^{1}H NMR (200MHz, d_6-DMSO) δ 13.55 (1H, bs), 11.00 (1H, s), 8.34 (1H, s), 8.17 (1H, d), 8.05 (1H, d), 7.49-7.78 (3H, m), 7.30 (2H, d).

INTERMEDIATE 5

1-(4-Amino-3-methylphenyl)-1-morpholin-4-yl-methanone

To a solution of 1-(3-methyl-4-nitrophenyl)-1-morpholin-4-yl-methanone (0.66g) in ethanol (30ml) was added 10% palladium on carbon (60mg) and the mixture stirred under an atmosphere of hydrogen for 2.5h. The reaction mixture was filtered through a Celite® pad and washed through with ethanol. The filtrate was concentrated *in vacuo* and evaporated *in vacuo* from hexane twice more to furnish the title compound (0.54g) as a pale pink solid.

^{1}H NMR (200MHz, d_6-DMSO) δ 7.22 (1H, s), 7.15 (1H, d), 6.66 (1H, d), 3.60-4.00 (10H, m), 2.20 (3H, s).

EXAMPLE 1

2-[3-(4-Chloro-3-nitrophenylsulfamoyl)benzoylamino]benzoic acid methyl ester

A solution of 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (0.20g) in dichloromethane (20ml) was stirred at room temperature. 4-Chloro-3-nitroaniline (0.12g) was added followed by pyridine (0.08ml) and the resulting mixture stirred overnight. The mixture was diluted with dichloromethane (20ml), washed with 2N hydrochloric acid (40ml), dried (magnesium sulfate) and the solvent removed *in vacuo* to give the title compound (0.31g) as a yellow foam.

TLC R_f 0.52 (50% ethyl acetate in hexane)

The following compounds were prepared in a similar manner.

EXAMPLE 2

2-[3-(4-Chloro-2-methylphenylsulfamoyl)benzoylamino]benzoic acid methyl ester

Prepared from 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (0.10g) and 4-chloro-2-methylaniline (0.048g) to give the title compound (0.10g) as a pink solid.

TLC R_f 0.73 (50% ethyl acetate in hexane)

EXAMPLE 3

2-[3-(2-Bromo-5-trifluoromethylphenylsulfamoyl)benzoylamino]-benzoic acid methyl ester

Prepared from 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (0.10g) and 2-bromo-5-(trifluoromethyl)aniline (0.14g) to give the title compound (0.13g) as a pink solid.

TLC R_f 0.65 (50% ethyl acetate in hexane)

EXAMPLE 4

2-[3-(2-Chloro-4-trifluoromethylphenylsulfamoyl)benzoylamino]-benzoic acid methyl ester

Prepared from 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (0.10g) and 4-amino-3-chlorobenzotrifluoride (0.11g) to give the title compound (0.13g) as a pink solid (0.13g).

TLC R_f 0.62 (50% ethyl acetate in hexane)

EXAMPLE 5

2-[3-(2,4-Dimethylphenylsulfamoyl)benzoylamino]benzoic acid methyl ester

Prepared from 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (100mg) and 2,4-dimethylaniline (0.07ml) to give the title compound (79mg) as a pink solid.

TLC R_f 0.41 (33% ethyl acetate in hexane)

EXAMPLE 6

2-[3-(4-Bromophenylsulfamoyl)benzoylamino]benzoic acid methyl ester

Prepared from 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (100mg) and 4-bromoaniline (50mg) to give the title compound (55mg) as a pink solid.

TLC R_f 0.50 (diethyl ether)

EXAMPLE 7

2-[3-(4-Bromo-2-trifluoromethylphenylsulfamoyl)benzoylamino] benzoic acid methyl ester

Prepared from 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (0.35g) and 2-amino-5-bromobenzotrifluoride (0.24g) to give the title compound (0.40g) as a gummy white solid.

TLC R_f 0.54 (diethyl ether)

EXAMPLE 8

2-[3-(2,4-Dichlorophenylsulfamoyl)benzoylamino]benzoic acid methyl ester

Prepared from 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (0.35g) and 2,4-dichloroaniline (0.16g) to give the title compound (0.46g) as a white solid.

TLC R_f 0.45 (diethyl ether)

EXAMPLE 9

2-[3-(2-Chloro-4-methylphenylsulfamoyl)benzoylamino]benzoic acid methyl ester

Prepared from 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (0.35g) and 2-chloro-4-methylaniline (0.12ml) to give the title compound (0.48g) as a white solid.

TLC R_f 0.53 (diethyl ether)

EXAMPLE 10

2-[3-(4-Chloronaphthalen-1-ylsulfamoyl)benzoylamino]benzoic acid methyl ester

Prepared from 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (0.35g) and 1-amino-4-chloronaphthalene (0.18g) to give the title compound (0.45g) as a white solid.

TLC R_f 0.50 (diethyl ether)

EXAMPLE 11

2-[3-(4-Hydroxycarbonyl-2-methylphenylsulfamoyl)benzoylamino] benzoic acid methyl ester

Prepared from 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (2.0g) and 4-amino-3-methylbenzoic acid (0.85g) to give the title compound (0.20g) as a white solid.
TLC R_f 0.50 (ethyl acetate)

EXAMPLE 12

2-[3-(4-Bromo-2-ethylphenylsulfamoyl)-benzoylamino]benzoic acid methyl ester

Prepared from 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (117mg) and 4-bromo-2-ethylaniline (66mg) to provide the title compound (165mg) as a red-brown solid.
TLC R_f 0.5 (50% ethyl acetate in hexane)
MS (ESI^+) 517, 519 (M+1)

EXAMPLE 13

2-{3-[2-Methyl-4-(morpholine-4-carbonyl)phenylsulfamoyl] benzoylamino}benzoic acid methyl ester

Prepared from 1-(4-amino-3-methylphenyl)-1-morpholin-4-yl-methanone (48mg) and 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (77mg) to afford the title compound (98mg) as an off-white solid.
TLC R_f 0.5 (50% ethyl acetate in hexane)
^1H NMR (200MHz, $CDCl_3$) δ 12.20 (1H, s), 8.85 (1H, d), 8.52 (1H, d), 8.23 (1H, d), 8.13 (1H, d), 8.00 (1H, d), 7.59-7.70 (2H, m), 7.28-7.37 (2H, m), 7.10-7.22 (3H, m), 4.00 (3H, s), 3.10-3.90 (8H, m), 2.10 (3H, s).

EXAMPLE 14

2-[3-(2-Methyl-6-trifluoromethylpyridin-3-ylsulfamoyl)benzoylamino]-benzoic acid methyl ester

Prepared from 3-amino-2-methyl-6-trifluoromethylpyridine (75mg) and 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (150mg) to give the title compound (113mg) as a white foam.
TLC R_f 0.6 (50% ethyl acetate in hexane)
^1H NMR (200MHz, $CDCl_3$) δ 12.24 (1H, s), 8.88 (1H, d), 8.52 (1H, s), 8.30 (1H, d), 8.13 (1H, dd), 7.90-8.05 (2H, m), 7.61-7.75 (2H, m), 7.55 (1H, d), 7.20 (1H, t), 7.10 (1H, s), 4.02 (3H, s), 2.48 (3H, s).

EXAMPLE 15

2-[3-(4-Chlorophenylsulfamoyl)benzoylamino]benzoic acid methyl ester

Prepared from 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (200mg) and 4-chloroaniline (140mg) to give the title compound (52mg) as a white solid.

TLC R_f 0.6 (50% ethyl acetate in hexane)

^{1}H NMR (400MHz, $CDCl_3$) δ 12.15 (1H, s), 8.79 (1H, d), 8.61 (1H, s), 8.18 (1H, d), 8.07 (1H, d), 7.92 (1H, d), 7.86 (1H, s), 7.55-7.62 (2H, m), 7.10-7.20 (5H, m).

EXAMPLE 16

2-[3-(2-Methyl-4-fluorophenylsulfamoyl)-benzoylamino]benzoic acid methyl ester

Prepared from 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (100mg) and 4-fluoro-2-methylaniline (39mg). The residue was purified by column chromatography on silica eluting with 50% ethyl acetate in hexane to yield the title compound (110mg) as an off-white solid.

R_f 0.4 (50% ethyl acetate in hexane)

MS 443 (M+H)

^{1}H NMR (200MHz, $CDCl_3$) δ 2.10 (s, 3H), 4.00 (s, 3H), 6.70 (s, 1H), 6.65-6.90 (m, 2H), 7.10-7.25 (m, 2H), 7.60 (t, 2H), 7.85 (d, 1H), 8.10 (d, 1H), 8.20 (d, 1H), 8.55 (s, 1H), 8.90 (d, 1H), 12.30 (s, 1H).

EXAMPLE 17

2-({1-[3-(4-Trifluoromethylphenylsulfamoyl)phenyl]methanoyl} amino)benzoic acid methyl ester

Prepared from 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (100mg) and 4-aminobenzotrifluoride (91mg) to yield the title compound (120mg) as an off-white solid.

R_f 0.62 (50% ethyl acetate in hexane)

^{1}H NMR (200MHz, d_6-DMSO) δ 3.85 (s, 3H), 7.20-7.40 (m, 3H), 7.55-7.70 (m, 3H), 7.80 (t, 1H), 7.95-8.10 (m, 2H), 8.20 (d, 1H), 8.30-8.50 (m, 2H), 11.10 (s, 1H), 11.50 (s, 1H).

EXAMPLE 18

2-({1-[3-(3-Chlorophenylsulfamoyl)phenyl]methanoyl}amino)benzoic acid methyl ester

Prepared from 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (100mg) and 3-chloroaniline (36mg) to yield the title compound (41mg) as an off white solid.
MS 445 (M+H)
^{1}H NMR (200MHz, $CDCl_3$) δ 3.95 (s, 3H), 7.00-7.20 (m, 5H), 7.55-7.65 (m, 2H), 8.00 (d, 1H), 8.10 (d, 1H), 8.65 (s, 1H), 8.80-8.85 (m, 2H), 12.20 (s, 1H).

EXAMPLE 19

2-[3-(4-Ethylcarbamoyl-2-methylphenylsulfamoyl)benzoylamino]-benzoic acid methyl ester

A solution of 2-[3-(4-hydroxycarbonyl-2-methylphenylsulfamoyl)benzoyl-amino]benzoic acid methyl ester (40mg) in dichloromethane (5ml) was stirred at room temperature. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (20mg) was added followed by ethylamine (2M solution in tetrahydrofuran, 0.05ml) and the resulting mixture stirred overnight. Washing with water (20ml) and saturated sodium bicarbonate solution (20ml), drying (magnesium sulfate) and removal of the solvent *in vacuo* gave a yellow solid. Purification by wet flash chromatography on silica eluting with diethyl ether gave the title compound (30mg) as a white solid.
TLC R_f 0.20 (diethyl ether)

EXAMPLE 20

3-[3-(4-Chlorophenylsulfamoyl)benzoylamino]benzoic acid methyl ester

A mixture of 3-(4-chlorophenylsulfamoyl)benzoic acid (100mg), methyl 3-aminobenzoate (48mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (92mg) in dichloromethane (15ml) was stirred at room temperature under an atmosphere of nitrogen for 3.5h. Wet flash chromatography on silica eluting with 50% ethyl acetate in hexane followed by washing with 2N hydrochloric acid (100ml) and brine (80ml), drying (magnesium sulfate) and removal of the solvent *in vacuo* gave the title compound (100mg) as a white solid.
TLC R_f 0.53 (50% ethyl acetate in hexane)

The following compound was prepared by a similar procedure.

EXAMPLE 21

2-Chloro-3-({1-[3-(4-trifluoromethylphenylsulfamoyl) phenyl]methanoyl}amino)benzoic acid methyl ester

Prepared from 3-(4-trifluoromethyl-phenylsulfamoyl)benzoic acid (100mg) and 2-chloro-3-aminobenzoic acid methyl ester (55mg) to afford the title compound (10mg) as a solid.

TLC R_f 0.5 (50% ethyl acetate in hexane)

MS (ESI^-) 511 (M-1)

EXAMPLE 22

3-(4-Chlorophenylsulfamoyl)-*N*-(2-cyanophenyl)benzamide

A suspension of 3-(4-chlorophenylsulfamoyl)benzoic acid (0.75g), in dichloromethane (100ml) was stirred at room temperature under an atmosphere of nitrogen. Oxalyl chloride (0.32ml) was added followed by 2 drops of DMF. The mixture was stirred for 2h before removal of the solvent *in vacuo*. Co-evaporation from hexane removed excess oxalyl chloride. The resulting residue was dissolved in dichloromethane (100ml); anthranilonitrile (0.34g) was added followed by pyridine (0.25ml). After stirring overnight the mixture was washed with 1N hydrochloric acid (2 x 50ml) and saturated sodium hydrogencarbonate solution (2 x 50ml), dried (magnesium sulfate) and the solvent removed *in vacuo*. Purification by wet flash chromatography on silica eluting with 10% ethyl acetate in dichloromethane gave the title compound (0.31g) as a white solid.

TLC R_f 0.45 (50% ethyl acetate in hexane)

EXAMPLE 23

4-[3-(2-Nitrophenylcarbamoyl)benzenesulfonylamino]benzoic acid *tert*-butyl ester

A solution of 3-(2-nitrophenylcarbamoyl)benzenesulfonyl chloride (250mg) in dichloromethane (15ml) was stirred at room temperature under an atmosphere of nitrogen. *Tert*-butyl-4-aminobenzoate (149mg) was added, followed by pyridine (0.09ml) and the reaction left to stir for 48h. The mixture was diluted with dichoromethane (30ml), washed with 2N hydrochloric acid (80ml) and saturated sodim hydrogencarbonate solution (80ml), dried (magnesium sulfate) and the solvent removed *in vacuo* to give a yellow solid. Purification by wet flash chromatography on silica

eluting with 33% hexane in ethyl acetate gave the title compound (172mg) as a yellow solid.

^{1}H NMR (200MHz, d_6-DMSO) δ 11.00-10.95 (2H, m), 8.40 (1H, s), 8.20 (1H, d), 8.10-8.00 (2H, m), 7.85-7.70 (5H, m), 7.50-7.40 (1H, m), 7.25 (2H, d), 1.50 (9H, s)

TLC R_f 0.37 (33% ethyl acetate in hexane)

EXAMPLE 24

4-[3-(2-Nitrophenylcarbamoyl)benzenesulfonylamino]benzoic acid

A solution of 4-[3-(2-nitrophenylcarbamoyl)benzenesulfonylamino]-benzoic acid *tert*-butyl ester (160mg) in a mixture of trifluoroacetic acid (2ml) and dichloromethane (10ml) was stirred at room temperature under an atmosphere of nitrogen for 50 minutes before removal of the solvent *in vacuo*. Co-evaporation from toluene to remove excess trifluoroacetic acid gave the title compound (139mg) as a yellow solid.

^{1}H NMR (200MHz, d6-DMSO) δ 12.85-12.60 (1H, b), 11.00 (2H, s), 8.45 (1H, s), 8.20 (1H, d), 8.10-8.00 (2H, m), 7.90-7.70 (5H, m), 7.55-7.45 (1H, m), 7.25 (2H, d)

TLC R_f 0.62 (ethyl acetate)

EXAMPLE 25

4-[3-(2-Nitrophenylcarbamoyl)benzenesulfonylamino]benzoic acid ethyl amide

A mixture of 4-[3-(2-nitrophenylcarbamoyl)benzenesulfonylamino]benzoic acid (132mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (86mg) and ethylamine (2.0M solution in tetrahydrofuran, 0.38ml) in dichloromethane (15ml) was stirred overnight at room temperature under an atmosphere of nitrogen. The mixture was diluted with 5% methanol in dichloromethane (20ml), washed with water (60ml) and 1N hydrochloric acid (60ml), dried (magnesium sulfate) and the solvent removed *in vacuo* to leave a yellow residue. Trituration with diethyl ether then purification by wet flash chromatography on silica eluting with ethyl acetate gave the title compound (19mg) as a yellow solid.

^{1}H NMR (200MHz, d_6-DMSO) δ 11.00 (1H, s), 10.80 (1H, s), 8.40 (1H, s), 8.35 (1H, t), 8.20 (1H, d), 8.05 -7.95 (2H, m), 7.85-7.65 (5H, m), 7.45 (1H, m), 7.15 (2H, d), 3.30-3.15 (2H, m), 1.05 (3H, t)

TLC R_f 0.62 (ethyl acetate)

EXAMPLE 26

2-[3-(4-Chloro-3-nitrophenylsulfamoyl)benzoylamino]benzoic acid

A suspension of 2-[3-(4-chloro-3-nitrophenylsulfamoyl)benzoylamino]-benzoic acid methyl ester (0.30g) in 50% aqueous tetrahydrofuran (20ml) was stirred at room temperature. Lithium hydroxide (0.13g) was added and the resulting mixture stirred overnight. The tetrahydrofuran was removed *in vacuo*, the residual aqueous portion was acidified with 2N hydrochloric acid and extracted with dichloromethane (3 x 20ml). The combined organic extracts were dried (magnesium sulfate) and the solvent removed *in vacuo*. Trituration with ether gave the title compound (0.15g) as an off-white solid.

^{1}H NMR (200MHz, d_6-DMSO) δ 8.65 (1H, d), 8.45 (1H, s), 8.20 (1H, d), 8.10-8.00 (2H, m), 7.90-7.60 (4H, m), 7.40 (1H, dd), 7.25 (1H, t),

TLC R_f 0.3 (50% ethyl acetate in hexane)

The following compounds were prepared in a similar manner.

EXAMPLE 27

2-[3-(4-Chloro-2-methylphenylsulfamoyl)benzoylamino]benzoic acid

Prepared from 2-[3-(4-chloro-2-methylphenylsulfamoyl)benzoylamino]-benzoic acid methyl ester (93mg) to give the title compound (35mg) as a white solid.

^{1}H NMR (200MHz, d_6-DMSO) δ 8.65 (1H, d), 8.30 (1H, s), 8.20 (1H, dm), 8.05 (1H, dt), 7. 90 -7. 75 (2H, m), 7.70 (1H, dt), 7.30-7.10 (3H, m), 7.00 (1H, d)

TLC R_f 0.6 (ethyl acetate)

EXAMPLE 28

2-[3-(2-Bromo-5-trifluoromethylphenylsulfamoyl)benzoylamino] benzoic acid

Prepared from 2-[3-(2-bromo-5-trifluoromethylphenylsulfamoyl)benzoyl-amino]benzoic acid methyl ester (0.14g) to give the title compound (0.12g) as a white solid.

^{1}H NMR (200MHz, d_6-DMSO) δ 8.65 (1H, d), 8.30 (1H, s), 8.20 (1H, d), 8.10 (1H, d), 7.95-7.80 (3H, m), 7.70 (1H, dt), 7.55 (1H, dd), 7.45 (1H, d), 7.35 (1H, dt)

TLC R_f 0.4 (50% ethyl acetate in hexane)

EXAMPLE 29

2-[3-(2-Chloro-4-trifluoromethylphenylsulfamoyl)benzoylamino] benzoic acid

Prepared from 2-[3-(2-chloro-4-trifluoromethylphenylsulfamoyl)benzoyl-amino]-benzoic acid methyl ester (120mg) to give the title compound (61mg) as an off white solid.

^{1}HMR (200MHz, d_6-DMSO) δ 8.65 (1H, d), 8.40 (1H, s), 8.35 (1H, d), 8.00-8.15 (2H, m), 7.00-7.90 (2H, m), 7.75-7.65 (2H, m), 7.55 (1H, d), 7.25 (1H, dt)

TLC R_f 0.70 (ethyl acetate)

EXAMPLE 30

2-[3-(2,4-Dimethylphenylsulfamoyl)benzoylamino]benzoic acid

Prepared from 2-[3-(2,4-dimethylphenylsulfamoyl)benzoylamino]benzoic acid methyl ester (72mg) to give the title compound (57mg) as an off white solid.

^{1}H NMR (200MHz, d_6-DMSO) δ 12.45 (1H, b), 9.65 (1H, s), 8.65 (1H, d), 8.30 (1H, s), 8.20 (1H, dd), 8.05 (1H, dd), 7.90-7.75 (2H, m), 7.70 (1H,dt), 7.25 (1H, t), 6.95 (1H, d), 6.90 (1H, dd), 6.80 (1H, d)

TLC R_f 0.4 (50% ethyl acetate in hexane)

EXAMPLE 31

2-[3-(4-Bromophenylsulfamoyl)benzoylamino]benzoic acid

Prepared from 2-[3-(4-bromophenylsulfamoyl)benzoylamino]benzoic acid methyl ester (50mg) to give the title compound (45mg) as a white solid.

^{1}H NMR (200MHz, $CDCl_3$) δ 12.55 (1H, s), 9.70 (1H, s), 9.85 (1H, d), 8.55 (1H, s), 8.20-8.10 (2H, m), 7.85 (1H, d), 7.60-7.45 (2H, m), 7.35-7.25 (2H, m), 7.15-7.00 (3H, m)

TLC R_f 0.33 (diethyl ether)

EXAMPLE 32

2-[3-(4-Bromo-2-trifluoromethylphenylsulfamoyl)benzoylamino] benzoic acid

Prepared from 2-[3-(4-bromo-2-trifluoromethylphenylsulfamoyl)-benzoylamino]benzoic acid methyl ester (0.58g) to give the title compound (0.45g) as a white solid.

^{1}H NMR (200MHz, $CDCl_3$) δ 12.55 (1H, s), 8.85 (1H, d), 8.55 (1H, s), 8.25 (1H, dd), 8.15 (1H, dd), 7.90 (1H, dd), 7.65-7.50 (5H, m), 7.10 (1H, dt)
MS (EI^-) 542 (M - H).

EXAMPLE 33

2-[3-(2,4-Dichlorophenylsulfamoyl)benzoylamino]benzoic acid

Prepared from 2-[3-(2,4-dichlorophenylsulfamoyl)benzoylamino]benzoic acid methyl ester (0.46g) to give the title compound (0.40g) as a white solid.

^{1}H NMR (200MHz, $CDCl_3$) δ 12.15 (1H, s), 8.90 (1H, d), 8.50 (1H, s), 8.30 (1H, dd), 8.30 (1H, dd), 7.90 (1H, dd), 7.75-7.60 (3H, m), 7.35 (1H, s), 7.30-7.15 (3H, m)
MS (EI^-) 463,465 (M - H)

EXAMPLE 34

2-[3-(2-Chloro-4-methylphenylsulfamoyl)benzoylamino]benzoic acid

Prepared from 2-[3-(2-chloro-4-methylphenylsulfamoyl)benzoylamino]-benzoic acid methyl ester (0.44g) to give the title compound (0.38g) as a white solid.

^{1}H NMR (200MHz, $CDCl_3$) δ 12.55 (1H, s), 8.80 (1H, d), 8.45 (1H, d), 8.20 (1H, dd), 8.10 (1H, dd), 7.85-7.75 (2H, m), 7.60–7.40 (3H, m), 7.10 (1H, dt), 7.00 -6.95 (2H, m)
MS (EI^-) 443, 445(M – H)

EXAMPLE 35

2-[3-(4-Chloronaphthalen-1-ylsulfamoyl)benzoylamino]benzoic acid

Prepared from 2-[3-(4-chloronaphthalen-1-ylsulfamoyl)benzoylamino]-benzoic acid methyl ester (0.40g) to give the title compound (0.35g) as a white solid.

^{1}H NMR (200MHz, d_6-DMSO) δ 12.25 (1H, b), 10.60 (1H, b), 8.85 (1H, dd), 8.60 (1H, d), 8.40 (1H, dd), 8.30 (1H, d), 8.15 (1H, dd), 8.05 (1H, dd), 7.90-7.80 (2H, m), 7.75. -7.60 (3H, m), 7.45 (1H, dd), 7.30-7.20 (2H, m)
TLC R_f 0.4 (diethyl ether)

EXAMPLE 36

2-[3-(4-Ethylcarbamoyl-2-methylphenylsulfamoyl)benzoylamino]

benzoic acid

Prepared from 2-[3-(4-ethylcarbamoyl-2-methylphenylsulfamoyl)benzoyl-amino]benzoic acid methyl ester (30mg) to give the title compound (25mg) as a white solid.

^{1}H NMR (400MHz, d_6-DMSO) δ 12.40 (1H, b), 9.65 (1H, dd), 8.35-8.30 (2H, d), 8.20 (1H, dd), 8.05 (1H, dd), 7.90 (1H, dd), 7.80 (1H, dt), 7.70 (1H, dt), 7.55 (1H, dd), 7.20 (1H, dt), 7.10 (1H, d)

TLC R_f 0.15 (diethyl ether)

EXAMPLE 37

3-[3-(4-Chlorophenylsulfamoyl)benzoylamino]benzoic acid

Prepared from 3-[3-(4-chlorophenylsulfamoyl)benzoylamino]benzoic acid methyl ester (92mg) to give the title compound (53mg) as a white solid.

^{1}H NMR (200MHz, d_6-DMSO) δ 10.70 (1H, s), 8.40 (2H, s), 8.25 (1H, d), 8.05 (1H, d), 7.95 (1H, d), 7.80–7.70 (2H, m), 7.5 (1H, t), 7.30 (2H, d), 7.15 (2H, d)

TLC R_f 0.3 (50% ethyl acetate in hexane)

EXAMPLE 38

2-[3-(4-Bromo-2-ethylphenylsulfamoyl)benzoylamino]benzoic acid

Prepared from 2-[3-(4-bromo-2-ethyl-phenylsulfamoyl)-benzoylamino]-benzoic acid methyl ester (145mg) to provide the title compound (75mg) as an off-white solid.

TLC R_f 0.5 (50% ethyl acetate in hexane)

^{1}H NMR (200MHz, d_6-DMSO) δ 8.64 (1H, d), 8.37 (1H, s), 8.25 (1H, d), 8.05 (1H, d), 7.69-7.85 (2H, m), 7.22-7.40 (3H, m), 7.02 (1H, t), 6.83 (1H, d), 2.50 (2H, q), 0.94 (3H, t).

EXAMPLE 39

2-{3-[2-Methyl-4-(morpholine-4-carbonyl)phenylsulfamoyl] benzoylamino}benzoic acid

Prepared from 2-{3-[2-methyl-4-(morpholine-4-carbonyl)phenylsulfamoyl]benzoylamino}-benzoic acid methyl ester (80mg) to give the title compound (25mg) as a white solid.

MS (ESI$^+$) 524 (M+1)

^{1}H NMR (400MHz, d_6-DMSO) δ 12.35 (1H, bs), 9.95 (1H, s), 8.62 (1H, d), 8.25 (1H, s), 8.21 (1H, d), 8.07 (1H, d), 7.95 (1H, d), 7.82 (1H, t), 7.68

(1H, t), 7.14-7.27 (3H, m), 7.05 (1H, d), 6.58 (1H, bs), 3.15-3.65 (8H, m), 2.03 (3H, s).

EXAMPLE 40

2-[3-(2-Methyl-6-trifluoromethyl-pyridin-3-ylsulfamoyl)benzoylamino] benzoic acid

Prepared from 2-[3-(2-methyl-6-trifluoromethyl-pyridin-3-ylsulfamoyl)-benzoylamino]benzoic acid methyl ester (55mg) to provide the title compound (40mg) as a white solid.

TLC R_f 0.25 (50% ethyl acetate in hexane)

^{1}H NMR (200MHz, d_6-DMSO) δ 12.30 (1H, s), 8.62 (1H, d), 8.36 (1H, s), 8.24 (1H, d), 7.94-8.10 (2H, m), 7.63-7.89 (4H, m), 7.25 (1H, t), 2.31 (3H, s).

EXAMPLE 41

2-[3-(4-Chlorophenylsulfamoyl)benzoylamino]benzoic acid

Prepared from 2-[3-(4-chlorophenylsulfamoyl)benzoylamino]benzoic acid methyl ester (200mg) to provide the title compound (80mg) as a white solid.

TLC R_f 0.53 (ethyl acetate)

^{1}H NMR (400MHz, d_6-DMSO) δ 13.92 (1H, bs), 12.33 (1H, bs), 10.65 (1H, s), 8.64 (1H, dd), 8.39 (1H, s), 8.19 (1H, d), 8.08 (1H, d), 7.97 (1H, d), 7.80 (1H, t), 7.69 (1H, t), 7.33 (2H, d), 7.25 (1H, t), 7.15 (2H, d).

EXAMPLE 42

2-({1-[3-(3-Chlorophenylsulfamoyl)phenyl]methanoyl}amino)benzoic acid

Prepared from 2-({1-[3-(3-chloro-phenylsulfamoyl)-phenyl]-methanoyl}-amino)-benzoic acid methyl ester (41mg) to yield the title compound (20mg) as an off white solid.

R_f 0.14 (50% ethyl acetate in hexane)

^{1}H NMR (200MHz, d_6-DMSO) δ 7.00-7.20 (m, 5H), 7.55-7.65 (m, 2H), 7.90 (d, 1H), 8.05-8.25 (m, 1H), 8.65 (s, 1H), 8.80-8.85 (m, 2H).

EXAMPLE 43

2-({1-[3-(4-Trifluoromethylphenylsulfamoyl)phenyl]methanoyl} amino)benzoic acid

Prepared from 2-({1-[3-(4-trifluoromethyl-phenylsulfamoyl)-phenyl]-methanoyl}-amino)-benzoic acid methyl ester (120mg) to yield the title compound (110mg) as an off-white solid.

R_f 0.33 (50% ethyl acetate in hexane)

^{1}H NMR (200MHz, d_6-DMSO) δ 3.85 (s, 3H), 7.15-7.40 (m, 3H), 7.60-7.70 (m, 3H), 7.80 (t, 1H), 7.95-8.10 (m, 2H), 8.20 (d, 1H), 8.45 (s, 1H), 8.65 (d, 1H), 11.10 (s, 1H), 11.50 (s, 1H).

EXAMPLE 44

2-[3-(2-Methyl-4-fluorophenylsulfamoyl)benzoylamino]benzoic acid

Prepared from 2-[3-(2-methyl-4-fluorophenylsulfamoyl)benzoylamino] benzoic acid methyl ester (70mg) to yield the title compound (52mg) as an off white solid.

R_f 0.1 (50% ethyl acetate in hexane)

^{1}H NMR (200MHz, d_6-DMSO) δ 2.00 (s, 3H), 6.90-7.10 (m, 3H), 7.25 (t, 1H), 7.60-7.90 (m, 3H), 7.65 (t, 2H), 8.05 (d, 1H), 8.20 (d, 1H), 8.65 (d, 1H), 9.85 (s, 1H), 12.30 (s, 1H).

EXAMPLE 45

***N*-(2-Nitrophenyl)-3-(pyridin-3-ylsulfamoyl)benzamide**

A solution of 3-(2-nitrophenylcarbamoyl)benzenesulfonyl chloride (200mg) in dichloromethane (20ml) was stirred at room temperature under nitrogen. 3-Aminopyridine (66mg) and pyridine (0.06ml) were added and the reaction left to stir for 60h. The solvent was removed *in vacuo* and the residue purified by wet flash chromatography on silica eluting with ethyl acetate then 1% methanol in ethyl acetate to give the title compound (150mg) as a yellow solid.

^{1}H NMR (200MHz, d_6-DMSO) δ 11.00 (1H, s), 10.75 (1H, s), 8.35-8.15 (4H, m), 8.05 -7.95 (2H, m), 7.85-7.65 (3H, m), 7.60-7.40 (2H, m), 7.35-7.25 (1H, m)

TLC R_f 0.72 (ethyl acetate)

EXAMPLE 46

3-(4-Chlorophenylsulfamoyl)-*N*-[2-(1*H*-tetrazol-5-yl)phenyl] benzamide

A solution of 3-(4-chlorophenylsulfamoyl)-*N*-(2-cyanophenyl)benzamide (0.25g) in DMF (10ml) was stirred at 50°C. Sodium azide (79mg) and ammonium chloride (65mg) were added and stirring continued at 50°C

overnight. The mixture was cooled, diluted with ice (50ml) and acidified with concentrated hydrochloric acid. The resulting solid was collected by filtration and washed with water to give the title compound as a white solid (0.22g).

^{1}H NMR (400MHz, d_6-DMSO) δ 11.45 (1H, s), 10.65 (1H, s), 8.40 (1H, s), 8.35 (1H, d), 8.30 (1H, d), 8.05-7.95 (2H, m), 8.85 (1H, t), 7.65 (1H, t), 7.45 (1H, t), 7.30 (2H, d), 7.15 (2H, d)

MS (EI$^+$) 456 (M+H).

EXAMPLE 47

5-Methoxy-2-({1-[3-(4-trifluoromethylphenylsulfamoyl)phenyl] methanoyl}amino)benzoic acid

A solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (83mg) in dichloromethane (2ml) was added to a suspension of 3-(4-trifluoromethyl-phenylsulfamoyl)benzoic acid (100mg) and 5-methoxy-2-aminobenzoic acid methyl ester (54mg) in dichloromethane (2ml) and the reaction mixture was stirred for 18h under an atmosphere of nitrogen. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (30ml) and 0.7M hydrochloric acid (30ml). The organic phase was concentrated *in vacuo*; diethyl ether (5ml), dichloromethane (5ml) were added followed by hexane (50ml) to induce crystallization. The mixture was concentrated *in vacuo* to half of its original volume; the mother liquor was decanted and the solid material dried. This process was repeated to afford 5-methoxy-2-({1-[3-(4-trifluoromethyl-phenylsulfamoyl)-phenyl]-methanoyl}amino)benzoic acid methyl ester. A solution of this ester (47mg) and lithium hydroxide monohydrate (20mg) in tetrahydrofuran (2ml) and water (2ml) was stirred for 24h at room temperature. The reaction mixture was diluted with water (10ml) and extracted with dichloromethane (2 x 5ml). The aqueous phase was acidified with 2N hydrochloric acid and extracted with ethyl acetate (20ml). The organic phase was dried (magnesium sulfate) and concentrated *in vacuo* to provide the title compound (59mg).

TLC R_f 0.2 (50% ethyl acetate in hexane)

^{1}H NMR (200MHz, d_6-DMSO) δ 12.64 (1H, bs), 8.40-8.52 (2H, m), 8.17 (1H, d), 8.01 (1H, d), 7.78 (1H, t), 7.50-7.65 (3H, m), 7.18-7.35 (3H, m), 3.78 (3H, s).

The following compound was prepared by a similar procedure.

EXAMPLE 48

3-Nitro-5-({1-[3-(4-trifluoromethylphenylsulfamoyl)phenyl] methanoyl}amino)benzoic acid

Prepared from 3-(4-trifluoromethylphenylsulfamoyl)benzoic acid (100mg) and 3-nitro-5-aminobenzoic acid methyl ester (58mg) to provide the title compound (22mg).

TLC R_f 0.2 (50% ethyl acetate in hexane)

^{1}H NMR (200MHz, CD_3OD) δ 8.96 (1H, s), 8.70 (1H, s), 8.40-8.57 (2H, m), 8.18 (1H, d), 8.02 (1H, d), 7.60-7.75 (1H, m), 7.53 (2H, d), 7.31 (2H, d).

EXAMPLE 49

4-[3-(2-Chlorophenylcarbamoyl)benzenesulfonylamino]benzoic acid ethyl ester

A mixture of 3-(chlorosulfonyl)benzoyl chloride (500mg), 2-chloroaniline (0.22ml) and pyridine (0.17ml) in dichloromethane (20ml) was stirred at room temperature under a nitrogen atmosphere for 4.5h. The reaction mixture was diluted with dichloromethane, washed with 1N hydrochloric acid, dried (magnesium sulfate) and concentrated *in vacuo*. The residue was dissolved in dichloromethane (20ml), ethyl-4-aminobenzoate (347mg) was added and the reaction mixture was stirred at room temperature under an atmosphere of nitrogen for 20h. The reaction mixture was diluted with dichloromethane, washed with 2N hydrochloric acid, dried (magnesium sulfate) and concentrated *in vacuo* to give the title compound as an off-white solid after purification by preparative HPLC.

MS (ES+) 460 (M+1)

The following compound was prepared by a similar procedure.

EXAMPLE 50

4-[3-(2-Methoxyphenylcarbamoyl)benzenesulfonylamino]benzoic acid methyl ester

Prepared from 3-(chlorosulfonyl) benzoyl chloride (500mg), *o*-anisidine (0.24ml) and ethyl 4-aminobenzoate (347mg) to give the title compound after purification by preparative HPLC.

MS (ES^+) 455.7 (M+1)

EXAMPLE 51

3-[3-(4-Chlorophenylsulfamoyl)benzoylamino]benzamide

To a suspension of 3-(4-chlorophenylsulfamoyl)benzoic acid (100mg) in dichloromethane (10ml) was added oxalyl chloride (0.03ml) and DMF (5 drops). The reaction mixture was stirred for 30 minutes at room temperature under a nitrogen atmosphere. The solvent was removed *in vacuo* and the residue evaporated from toluene to afford the acid chloride as a yellow residue. To a solution of the latter in dichloromethane (10ml) was added 3-aminobenzamide (44mg) and pyridine (0.05ml) and the reaction mixture stirred at room temperature for 1.5h. The mixture was diluted with dichloromethane (30ml), washed with 2N hydrochloric acid (70ml) and saturated aqueous sodium hydrogencarbonate solution (70ml), dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica, eluting with ethyl acetate to afford the title compound (10mg) as a white solid.

TLC R_f 0.4 (ethyl acetate)

^1H NMR (200MHz, $CDCl_3$) δ 9.96 (1H, bs), 8.35 (1H, s), 8.10 (1H, d), 7.89-7.98 (2H, m), 7.80 (1H, d), 7.36-7.61 (3H, m), 7.15 (2H, d), 7.03 (2H, d).

The following compounds were prepared by a similar procedure.

EXAMPLE 52

3-(4-Chlorophenylsulfamoyl)-*N*-(2-methanesulfonylphenyl)benzamide

Prepared from 3-(4-chlorophenylsulfamoyl)benzoic acid (330mg) and 2-methylsulfonylaniline (207mg). Purification by flash chromatography on silica, eluting with 50% ethyl acetate in hexane afforded the title compound (311mg) as a white solid.

TLC R_f 0.3 (50% ethyl acetate in hexane)

^1H NMR (200MHz, d_6-DMSO) δ 10.59 (1H, s), 8.34 (1H, s), 8.09-8.19 (2H, m), 7.94-8.03 (2H, m), 7.74-7.86 (2H, m), 7.47-7.58 (1H, m), 7.34 (2H, d), 7.14 (2H, d), 3.30 (3H, s).

EXAMPLE 53

***N*-(2-Acetylphenyl)-3-(4-chlorophenylsulfamoyl)benzamide**

Prepared from 3-(4-chlorophenylsulfamoyl)benzoic acid (311mg) and 2'-aminoacetophenone (135mg). Purification by flash chromatography on silica eluting with 50% ethyl acetate in hexane gave the title compound (363mg) as a white solid.

TLC R_f 0.28 (50% ethyl acetate in hexane)

^{1}H NMR (200MHz, d_6-DMSO) δ 12.35 (1H, s), 10.65 (1H, s), 8.54 (1H, d), 8.35 (1H, s), 8.09-8.12 (2H, m), 7.99 (1H, d), 7.81 (1H, t), 7.70 (1H, t), 7.27-7.38 (3H, m), 7.10-7.17 (2H, m), 2.70 (3H, s).

EXAMPLE 54

3-(4-Chlorophenylsulfamoyl)-*N*-[2-(1-hydroxyiminoethyl)phenyl] benzamide

A mixture of *N*-(2-acetylphenyl)-3-(4-chlorophenylsulfamoyl)benzamide 192mg), hydroxylamine hydrochloride (73mg) and sodium acetate (96mg) in ethanol (10ml) and water (3ml) was heated at 100°C for 75 minutes, then allowed to cool to room temperature. The reaction mixture was diluted with water (20ml) and extracted with ethyl acetate (2 x 25ml). The combined organic phases were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica eluting with 50% ethyl acetate in hexane to give the title compound (139mg) as a white solid.

TLC R_f 0.35 (50% ethyl acetate in hexane)

^{1}H NMR (400MHz, d_6-DMSO) δ 11.77 (1H, s), 11.63 (1H, s), 10.60 (1H, s), 8.38 (1H, s), 8.33 (1H, d), 8.12 (1H, d), 7.95 (1H, d), 7.75 (1H, t), 7.63 (1H, d), 7.43 (1H, t), 7.32 (2H, d), 7.25 (1H, t), 7.13 (2H, d), 2.24 (3H, s).

EXAMPLE 55

3-(4-Chlorophenylsulfamoyl)-*N*-pyridin-2-yl-benzamide

To a suspension of 3-(4-chlorophenylsulfamoyl)benzoic acid (100mg) in dichloromethane (10ml) was added oxalyl chloride (0.03ml) and DMF (5 drops). The reaction mixture was stirred for 30 minutes at room temperature under a nitrogen atmosphere. The solvent was removed *in vacuo* and the residue evaporated from toluene to afford the acid chloride as a yellow residue. Sodium hydride (60% dispersion in mineral oil, 18mg) was added to a solution of 2-aminopyridine (36mg) in *N,N*-

dimethylformamide (10ml) and stirred for 0.5h. A solution of the acid chloride in *N,N*-dimethylformamide (5ml) was then added to the reaction mixture and stirring was continued for a further18h. The solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate (30ml) and water (60ml). The organic phase was washed with brine, dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica eluting with ethyl acetate to afford the title compound (7mg) as a white solid.

TLC R_f 0.8 (ethyl acetate)

^{1}H NMR (200MHz, 10% CD_3OD in $CDCl_3$) δ 8.25-8.40 (3H, m), 8.09-8.15 (1H, m), 7.74-7.85 (2H, m), 7.54 (1H, t), 7.00-7.18 (5H, m).

EXAMPLE 56

3-[3-(4-Chlorophenylsulfamoyl)benzoylamino]-*N*-hydroxybenzamide

To a solution of 2-[3-(4-chlorophenylsulfamoyl)benzoylamino]benzoic acid (120mg) in dichloromethane (10ml) was added *tert*-butyldimethylsilylhydroxylamine (62mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (81mg). The reaction mixture was stirred for 1.5h at room temperature under a nitrogen atmosphere. The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica to furnish *N*-(4-chlorophenyl)-3-(4-oxo-4*H*-benzo[D][1,3]oxazin-2-yl)benzenesulfonamide (95mg) as a white solid. To a solution of the oxazine (80mg) in tetrahydrofuran (5ml) was added hydroxylamine (50% aqueous solution, 1ml) and the reaction mixture heated at reflux for 10 minutes. The reaction mixture was cooled to room temperature, diluted with water (20ml) and extracted with ethyl acetate (3 x 20ml). The combined organic phases were washed with brine (30ml), dried (magnesium sulfate) and concentrated *in vacuo* to provide the title compound (35mg) as a white solid.

TLC R_f 0.75 (ethyl acetate)

^{1}H NMR (200MHz, d_6-DMSO) δ 12.43 (1H, s), 9.42 (1H, bs), 8.54 (1H, d), 8.37 (1H, s), 8.13 (1H, d), 7.96 (1H, d), 7.80 (1H, t), 7.70 (1H, d), 7.59 (1H, t), 7.33 (1H, d), 7.22 (1H, t), 7.15 (2H, d).

EXAMPLE 57

2-[3-(2-Methyl-5-trifluoromethylphenylsulfamoyl)benzoylamino] benzoic acid.

A solution of 2-(3-chlorosulfonylbenzoylamino)benzoic acid methyl ester (100mg) in dichloromethane (5ml) was treated with 3-amino-4-methylbenzotrifluoride (100mg) and pyridine (0.46ml). The mixture was stirred at room temperature for 12h and then diluted with dichloromethane (40ml). The organic solution was washed with 2M hydrochloric acid, dried (magnesium sulfate) and filtered. The filtrate was evaporated *in vacuo* to yield a colourless gum. The residue was dissolved in tetrahydrofuran and treated with a solution of lithium hydroxide (59mg) in water (10ml). The mixture was stirred for 12h and then the organic solvent removed *in vacuo*. The residue was washed with dichloromethane (2 x 20ml), acidified with 2M hydrochloric acid and extracted with dichloromethane (3 x 30ml). The extracts were combined, dried (magnesium sulfate) and filtered. The filtrate was evaporated *in vacuo* to yield the title compound (120mg) as an off-white solid.

R_f 0.66 (ethyl acetate)

MS 479 (M+H)

^{1}H NMR (200MHz, d_6-DMSO) δ 2.10 (s, 3H), 3.85 (s, 3H), 7.10-7.32 (m, 2H), 7.35-7.55 (m, 2H), 7.6-7.90 (m, 3H), 8.05 (d, 1H), 8.15-8.30 (m, 2H), 8.65 (d, 1H), 10.10 (s, 1H), 12.30 (s, 1H).

BIOLOGICAL ACTIVITY

The following assay can be used to demonstrate the activity of compounds according to the invention:

Measurement of Cyclic AMP PDE Activity

PDE7 hydrolyses cAMP to 5'AMP, a linear nucleotide. The assay used to determine this activity is based on the observation that linear nucleotides bind preferentially to SPA yttrium silicate beads, compared to cyclic nucleotides, in the presence of zinc sulphate. The 5'AMP, the product, therefore binds directly to the beads and cAMP does not. The binding of the radiolabelled product to the bead brings it into close enough proximity to allow tritium to excite the scintillant in the bead.

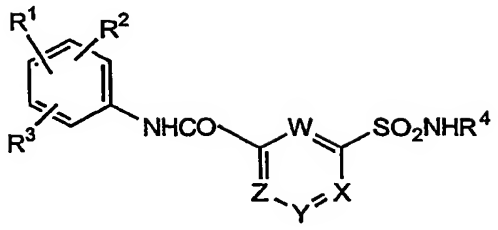
The PDE7 assay was carried out using Amersham Pharmacia SPA technology (Amersham Pharmacia Biotech). The assay was buffered with

50mM Tris containing 8.3mM $MgCl_2$ and 1.7mM EGTA pH 7.5. Assay buffer, inhibitor, cAMP 0.029μM, final) and ^{3}H-cAMP (~5nM, final concentration) were pipetted into a 96 well microtitre plate. The reaction was initiated with the addition of 20μl of PDE7 enzyme [see Michaeli, T *et al* (1993) J. Biol. Chem. 268, 12925-12932] to give a final volume of 100μl. The assay was incubated for 30 minutes at 30°C. The reaction was terminated by the addition of 50μl SPA yttrium silicate beads. The plates were then sealed, mixed and counted on a Packard TopCount scintillation counter (Canberra Packard).

In this assay, compounds according to the invention have IC_{50} values of around 10μM and less, typically around 1μM and less.

CLAIMS

1. A compound of formula (1):



(1)

wherein

W, X, Y and Z which may be the same or different, each represents a nitrogen atom or a $C(R^5)$ group [in which R^5 is a hydrogen or halogen atom or an alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, $-NO_2$ or -CN group] provided that two or more of W,X,Y and Z are $C(R^5)$ groups;

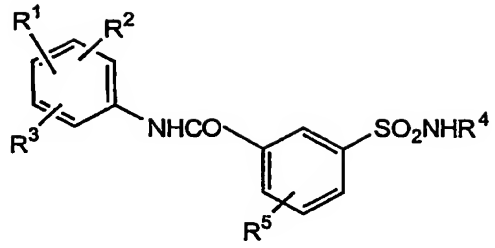
R^1, R^2 and R^3, which may be the same or different, each is an atom or group $-L^1(Alk^1)_rL^2(R^6)_s$ in which L^1 and L^2, which may be the same or different, is each a covalent bond or a linker atom or group, r is zero or the integer 1, Alk^1 is an aliphatic or heteroaliphatic chain, s is an integer 1, 2 or 3 and R^6 is a hydrogen or halogen atom or a group selected from alkyl, $-OR^7$ [where R^7 is a hydrogen atom or an optionally substituted alkyl group], $-SR^7$, $-NR^7R^8$ [where R^8 is as just defined for R^7 and may be the same or different], $-NO_2$, -CN, $-CO_2R^7$, $-SO_3H$, $-S(O)R^7$, $-SO_2R^7$, $-OCO_2R^7$, $-CONR^7R^8$, $OCONR^7R^8$, $-CSNR^7R^8$, $-OCR^7$, $-OCOR^7$, $-N(R^7)COR^8$, $-N(R^7)CSR^8$, $-S(O)NR^7R^8$, $-SO_2NR^7R^8$, $-N(R^7)SO_2R^8$, $-N(R^7)CON(R^8)(R^9)$ [where R^9 is a hydrogen atom or an optionally substituted alkyl group], $-N(R^7)CSN(R^8)R^9$), $-N(R^7)SO_2N(R^8)(R^9)$, $-C(R^7)=NO(R^8)$, cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group]; provided that one or more of R^1, R^2 or R^3 is a substituent other than a hydrogen atom;

R^4 represents an optionally substituted phenyl, 1- or 2- naphthyl, pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl group;

and the salts, solvates, hydrates and N-oxides thereof;

provided that the compound of formula (1) is not 3-(4-bromophenylsulfamoyl)-*N*-(3-nitrophenyl)benzamide.

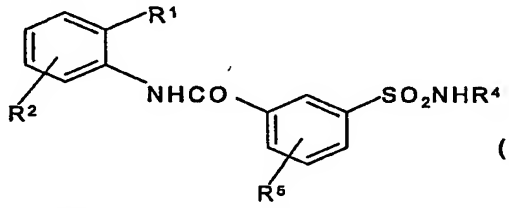
2. A compound according to Claim 1 of formula (1a):



(1a)

wherein R^1, R^2, R^3, R^4 and R^5 are as generally and particularly defined herein for compounds of formula (1);
and the salts, solvates, hydrates and N-oxides thereof.

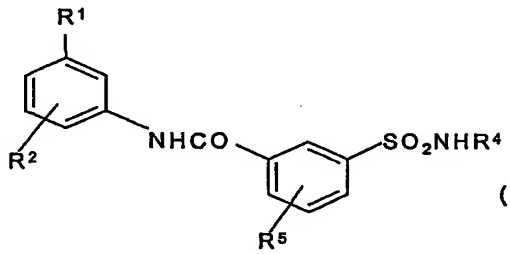
3. A compound according to Claim 1 or Claim 2 of formula (1b):



(1b)

wherein R^2, R^4 and R^5 are as generally and particularly defined herein for compounds of formula (1);
R^1 is a substituent, other than a hydrogen atom, as defined herein for compounds of formula (1);
and the salts, solvates, hydrates and N-oxides thereof.

4. A compound according to Claim 1 or Claim 2 of formula (1c):



(1c)

wherein R^2, R^4 and R^5 are as generally and particularly defined herein for compounds of formula (1);
R^1 is a substituent, other than a hydrogen atom, as defined herein for compounds of formula (1);
and the salts, solvates, hydrates and N-oxides thereof.

5. A compound according to any preceding Claim wherein R^5 is a hydrogen atom.

6. A compound according to any preceding Claim wherein R^4 is a substituted phenyl, 1- or 2- naphthyl, pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl group.

7. A compound according to Claim 5 wherein R^4 is a substituted phenyl, 1-naphthyl or pyridyl group.

8. A compound according to Claim 5 or 6 wherein R^4 is substituted by one or two R^{4a} substituents.

9. A compound according to any preceding Claim wherein R^1 is a $-CO_2H$, $-NO_2$ or tetrazolyl group.

10. A compound which is:
4-[3-(2-nitrophenylcarbamoyl)benzenesulfonylamino]benzoic acid *tert*-butyl ester;
4-[3-(2-nitrophenylcarbamoyl)benzenesulfonylamino]benzoic acid ethyl amide;
2-[3-(4-chloro-3-nitrophenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(4-chloro-2-methylphenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(2-bromo-5-trifluoromethylphenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(2-chloro-4-trifluoromethylphenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(2,4-dimethylphenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(4-bromophenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(4-bromo-2-trifluoromethylphenylsulfamoyl)benzoylamino] benzoic acid;
2-[3-(2,4-dichlorophenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(2-chloro-4-methylphenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(4-chloronaphthalen-1-ylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(4-ethylcarbamoyl-2-methylphenylsulfamoyl)benzoylamino] benzoic acid;

3-[3-(4-chlorophenylsulfamoyl)benzoylamino]benzoic acid;
and the salts, solvates, hydrates and N-oxides thereof.

11. A compound which is:
2-[3-(4-bromo-2-ethyl-phenylsulfamoyl)benzoylamino]benzoic acid;
2-[3-(2-methyl-6-trifluoromethyl-pyridin-3-ylsulfamoyl)benzoylamino] benzoic acid;
2-[3-(4-chlorophenylsulfamoyl)benzoylamino]benzoic acid;
2-({1-[3-(3-chlorophenylsulfamoyl)phenyl]methanoyl}amino)benzoic acid;
2-({1-[3-(4-trifluoromethylphenylsulfamoyl)phenyl]methanoyl}amino) benzoic acid;
2-[3-(2-methyl-4-fluorophenylsulfamoyl)benzoylamino]benzoic acid;
5-methoxy-2-({1-[3-(4-trifluoromethylphenylsulfamoyl)phenyl] methanoyl}amino)benzoic acid;
2-[3-(2-methyl-5-trifluoromethylphenylsulfamoyl)benzoylamino]benzoic acid;
and the salts, solvates, hydrates and N-oxides thereof.

12. A pharmaceutical composition comprising a compound according to Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

PATENT COOPERATION TREATY

PCT

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT

(PCT Article 17(2)(a), Rules 13ter.1(c) and Rule 39)

Applicant's or agent's file reference	IMPORTANT DECLARATION	Date of mailing *(day/month/year)*
REP06787WO		11/10/2001
International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/GB 01/02705	20/06/2001	20/06/2000
International Patent Classification (IPC) or both national classification and IPC		
Applicant		
CELLTECH CHIROSCIENCE LIMITED et al.		

This International Searching Authority hereby declares, according to Article 17(2)(a), that **no international search report will be established** on the international application for the reasons indicated below

1. ☐ The subject matter of the international application relates to:
   - a. ☐ scientific theories.
   - b. ☐ mathematical theories
   - c. ☐ plant varieties.
   - d. ☐ animal varieties.
   - e. ☐ essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes.
   - f. ☐ schemes, rules or methods of doing business.
   - g. ☐ schemes, rules or methods of performing purely mental acts.
   - h. ☐ schemes, rules or methods of playing games.
   - i. ☐ methods for treatment of the human body by surgery or therapy.
   - j. ☐ methods for treatment of the animal body by surgery or therapy.
   - k. ☐ diagnostic methods practised on the human or animal body.
   - l. ☐ mere presentations of information.
   - m. ☐ computer programs for which this International Searching Authority is not equipped to search prior art.

2. ☒ The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:
   ☒ the description ☒ the claims ☐ the drawings

3. ☐ The failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions prevents a meaningful search from being carried out:
   - ☐ the written form has not been furnished or does not comply with the standard.
   - ☐ the computer readable form has not been furnished or does not comply with the standard.

4. Further comments:

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Véronique Baillou

Form PCT/ISA/203 (July 1998)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 203

Not a single compound according to the examples (and to claims 10 and 11) falls within the scope of claim 1. It is therefore impossible to determine which subject-matter the applicant actually wants to have protected. Under these circumstances, the application is to be regarded as unclear to such an extent that no search is possible.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.